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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/786,505	GROSS ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5, 7-9, 16, 17, 37 and 40* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-8, 16-17, 37 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

In response to the Final Office Action dated 04/20/2007, applicants' filed an RCE received on 10/22/07 and a response to restriction requirement on 01/04/08 is acknowledged. In said RCE, applicants'amended claims 1, 7, 9, 16, 37 and 40 and in response to restriction requirement on 01/04/08, applicants' further amended claims 8, 9, 16 and 37 and elected with traverse Group I claims 1-5, 7, 8 and 40. In the response to restriction requirement on 01/04/08, applicants have argued that there would be no undue burden on the examiner to search claims 9, 16, 17 and 37 along with the elected Group I, claims 1-5, 7, 8 and 40. Applicants arguments have been considered and found to be persuasive to rejoin claims 16, 17 and 37 that are directed to the elected polynucleotide, however claim 9 will not be rejoined as said claim is directed to an anti-sense sequence and a search for the polynucleotide sequence of SEQ ID NO: 6 will not necessarily yield anti-sense molecules of SEQ ID NO: 6 and therefore would not be coextensive. Furthermore, examination of said claim 9 also requires consideration of scope of enablement and analysis of prior art. Hence, for the above cited reasons searching of all claims is a serious search burden and the request for reconsideration of the election/restriction requirement cannot be granted at this stage of the prosecution and therefore made FINAL.

Claims 1-5, 7-9, 16, 17, 37 and 40 are pending, claim 9 is withdrawn as said claim is drawn to non-elected invention and thus claims 1-5, 7, 8 16, 17, 37 and 40 are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn- New Matter-Claim Rejections 35 USC § 112

Previous rejection of claims 1, 7, 37 and 40 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement /new-matter is being withdrawn due to amendments to the claims and cancellation of the new-matter.

Maintained- New-Matter/Objection to Specification

The amendment filed on 02/07/2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The three paragraphs added to the specification on 02-08-07 are new matter. Support has not been provided for the new paragraphs and none can be found. In particular the phrase "configured to generate transgenically generated phospholipase A2 (TGiPLA2) mice" cannot be found. The scope of nucleic acid sequences configured as claimed was not contemplated in the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Applicants' have not addressed this issue in their replies dated 10/22/07 and 01/04/08.

Maintained-Claim Objections

Claims 37 and 40 are objected to due to the following informality: Said claims recite "iPLA$_2$", this is not a standard abbreviation for phospholipase A_2 (PLA$_2$). The abbreviation should be expanded at least in the first recitation.

Applicants' have not addressed this issue in their replies dated 10/22/07 and 01/04/08.

New-Claim Objections

Claim 8 is objected to due to the following informality: Claim 8 in line 2 recites "with 7", this is a typographical error and examiner suggests amending the claim to recite "with claim 7".

New-Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 (claims 4, 5, 16, 17, 37 depending therefrom), claim 7 (claim 8 depending therefrom) and claim 40 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 7 and 40 recite the phrase "….supplies at least one fatty acids for β-oxidation and hydrolyzing lipids for signaling molecule to regulate energy storage". At the outset the claim language is awkward and poor English. Furthermore, it is unclear what all it encompasses? As all fatty acids cannot undergo β-oxidation and require further modification to enter the β-oxidation cycle and similarly hydrolyzing lipids does not always yield signaling molecules, the metes and bounds of the claims are not clear to the examiner. Clarification is required.

Claim 16 (claim 17 depending therefrom) are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 recites the phrase "….suitable for generating a transgenic mouse..." What properties/limitations to the

vector is required to make it suitable for generating a transgenic mouse? Clarification is required.

Maintained-Claim Rejections: 35 USC § 112

Claims 1-2, 4-5, 7, 16-17 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide of SEQ ID NO: 6 encoding a polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, vector and isolated host cell comprising said polynucleotide, does not reasonably provide enablement for any polynucleotide encoding any phospholipase A2γ or any polynucleotide encoding a phospholipase A2γ wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6, vector and host cell comprising said polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Claims 1-2, 4-5, 7, 16-17 and 40 are so broad as to encompass any polynucleotide encoding any phospholipase A2γ or any polynucleotide encoding a phospholipase A2γ wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6, vector and host cell comprising said polynucleotide. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and encoding polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant

of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to a polynucleotide of SEQ ID NO: 6 encoding a polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, vector and isolated host cell comprising said polynucleotide, but provides no guidance with regard to the making of other variants and mutants or with regard to other uses. In view of the broad breadth of the claims, amount of experimentation required to make the claimed polynucleotides and encoding polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass all modifications of to any polynucleotide encoding any phospholipase A2γ or any polynucleotide

encoding a phospholipase A2γ wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6, because the specification does not establish: (A) regions of the polynucleotide/protein structure which may be modified without affecting the activity of encoded phospholipase A2γ ; (B) the general tolerance of the polynucleotide and the encoded polypeptide having phospholipase A2γ activity to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides with an enormous number of modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

While methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants capable of having phospholipase A2γ activity, requires that one of ordinary skill in the art know or be provided with guidance for the selection of which, of the infinite number of variants, have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of

producing and testing all of the virtually infinite possibilities. For the rejected claims, this would clearly constitute **undue** experimentation. Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(.66)^{\mathbf{X}}$ X 100% where **x** is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 90% sequence identity allows up to 342 mutations within the 3420 nucleotides of SEQ ID NO: 6. For argument sake, even if one assumes only 1/3 of the 342 nucleotide mutants/changes result in amino acid changes that result in mutations, the number of likely changes will be still around 114 amino acid changes and, thus, only $(0.66)^{114}$ X 100% equivalent to **2.6×10^{-19}%** of random mutants having 90% sequence identity to encoding polynucleotide of SEQ ID NO: 6 would be active. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would potentially allow for finding a reasonable number of active mutants within about a hundred thousand inactive mutants. But finding a few mutants within several trillions or more, as in the claim to 90% sequence identity to encoding polynucleotide of SEQ ID NO: 6 would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applying this estimate to the instant protein, a functional equivalent thereof with 90% sequence identity to encoding polynucleotide of SEQ ID NO: 6, as recited in claim 7, an extremely low number of active mutants will be present among an enormously large number of inactive mutants and as such screening for these active mutants would be burdensome and undue experimentation when there is no guidance provided in the specification. The remainder of the rejected claims are even broader than Claim 7 allowing any number of changes in the amino acid sequence.

Applicants' have traversed this rejection with the reasoning, the claimed invention is enabled due to the amendments to claims and deletion of the newly added subject matter in the claims and the broad scope of the claims has been narrowed by adding the limitation "supplying at least one of fatty acids for β-oxidation and hydrolyzing lipids for signaling molecules that regulate energy storage".

Applicants' arguments have been considered and found to be non-persuasive as pointed out in the above rejection and supported by scientific reasoning (see Guo et al., reference above), a functional equivalent thereof with 90% sequence identity to encoding polynucleotide of SEQ ID NO: 6, as recited in Claims 1-2, 4-5, 7, 16-17 and 40, an extremely low number of active mutants will be present among an enormously large number of inactive mutants and as such screening for these active mutants would be burdensome and undue experimentation when there is no guidance provided in the specification.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because, while claim 8 is enabling for an isolated host cell transformed with the synthetic nucleic acid as claimed, does not reasonably provide enablement for

transgenic multi-cellular organisms or host cells within a multi-cellular organism that have been transformed with the synthetic nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claim.

Claim 8 is so broad as to encompass transgenic multi-cellular organisms and host cells transformed with specific nucleic acids, including cells in *vitro* culture as well as within any multi-cellular organism. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to extremely large number of transformed organisms broadly encompassed by the claims. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multi-cellular organisms are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within the multi-cellular organism are unlikely to be applicable to transformation of other types of multi-cellular organism as multi-cellular organisms vary widely. However, in this case the disclosure is limited to only host cells *in vitro*. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of host cells within a multi-cellular organism for the production of polypeptide. The scope of claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA)). Without sufficient guidance, expression of genes in a particular host cell and having the desired biological characteristics is unpredictable, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and

undue. See *In re Wands* 858 F. 2d 731, 8 USPQ 2nd 1400 (Fed. Cir., 1988). It is suggested that the applicants limit the claim to " An isolated recombinant host cell …".

Written description

Claims 1-2, 4-5, 16-17 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2, 4-5, 16-17 and 40 (as interpreted), are directed to a genus of polynucleotides encoding polypeptides including variants, mutants and recombinants from any source having phospholipase A2γ activity with no support in the specification for the structural details associated with the function, vector and host cell comprising said polynucleotides. While the specification discloses the structure and characterization of the isolation of a polynucleotide with SEQ ID NO: 6 and encoding a polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, vector, host cell, method of making said polypeptide, the specification is silent in regard to (1) the structures and functions of all the polynucleotides and encoding polypeptides encompassed by the claims and (2) the critical structural elements of any variants, mutants, recombinants and truncated polypeptides having phospholipase A2γ activity from any source.

The genus of polynucleotides and encoding polypeptides required in the claimed invention is an extremely large structurally variable genus. While the argument can be made that the recited genus of polynucleotides and encoding polypeptides are adequately described by the disclosure of the structure of the of a polynucleotide with SEQ ID NO: 6 and encoding a

polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, since one could use structural homology to isolate those polynucleotides and encoding polypeptides recited in the claims, as taught by the art. Even highly structurally homologous polypeptides do not necessarily share the same function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999), teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8): 2405-2410, 2001), teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Furthermore, the targets that are being modulated by said polypeptides and the intended phenotype of transgenic mice expressing said polypeptides is completely undefined. Therefore, the claimed genera of polynucleotides and encoding polypeptides include proteins having widely variable structures, since minor changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polynucleotides and encoding polypeptides are encompassed by these claims. The specification only discloses a single species of the recited genus, the specification is silent regarding the targets that are modulated by said encoded polypeptides and the phenotype of transgenic mice expressing said polypeptide or the phenotype of the gene knockout mice wherein the expression of the polypeptide is eliminated. The disclosure is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all

species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants' have traversed this rejection with the reasoning, the amendments to claims and deletion of the newly added subject matter in the claims and the broad scope of the claims has been narrowed by adding the limitation "supplying at least one of fatty acids for β-oxidation and hydrolyzing lipids for signaling molecules that regulate energy storage" and therefore the written-description rejection should be withdrawn.

Applicants' arguments have been considered and found to be non-persuasive as pointed out in the above rejection and supported by scientific reasoning (see Witkowski et al., Seffernick et al., and Broun et al., references above), as there is clear evidence in the art that structurally similar molecules may not have similar functions and conversely functionally similar molecules may not have similar structures. Therefore, claims 1-2, 4-5, 7, 9, 16-17 and 40 (as interpreted), are directed to a genus of polynucleotides encoding polypeptides including variants, mutants and recombinants from any source having phospholipase A2γ activity with no support in the specification for the structural details associated with the function (as in claims 1-2, 4-5, 16-17 and 40) or an isolated polynucleotide sequence having at least 90% sequence identity to SEQ ID NO: 6 encoding a polypeptide having phospholipase A2γ activity (as in claim 7), vector and host cell comprising said polynucleotides.

Maintained-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-5, 16, 17 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al., (US Patent 5,625,125) when given the broadest interpretation. Claims 1-2, 4-5, 16, 17 and 40 are directed to any isolated polynucleotide encoding any phospholipase A2γ configured to generate transgenically generated phospholipase A2 mice, said phospholipase A2 catalyzes cleavage of fatty acid from sn-2 position of phospholipids, vector comprising said nucleic acid molecule and a cell transformed or transfected with said vector or an expression construct with a truncated version of phospholipase A2.

Bennett et al., (*supra)* disclose a vector comprising the isolated polynucleotide encoding the phospholipase A2 enzyme/polypeptide, the truncated version of the polypeptide and the use of the said vector in the generation of transgenic mice and rat expressing said polypeptides. Therefore the reference of Bennett et al., anticipates the claims 1-2, 4-5, 16, 17 and 40.

Applicants' have traversed this rejection with the reasoning, Bennett does not describe or suggest an isolated nucleic acid molecule as recited in claim 1. More specifically, Bennett does not describe or suggest an isolated nucleic acid molecule that supplies at least one of fatty acids for β-oxidation and hydrolyzing lipids for signaling molecules to regulate energy storage.

Applicants' arguments have been considered and found to be non-persuasive. Bennett et al., in column 1, lines 24-26 clearly state that Phospholipase A2s (PLA2s) are enzymes that catalyze the hydrolysis of the sn-2 fatty acyl ester bond of membrane phospholipids to yield a

free fatty acid, e. g., arachidonic acid and a lysophospholipid which are well known in the art as signaling molecules and are involved in modulating many cellular functions and further as admitted by the applicants' in the instant disclosure, page 2, first paragraph, lines 1-4. Examiner also takes the position that the signaling molecules generated by the catalytic activity of Phospholipase A2s (PLA2s) of Bennett et al., disclosure and the phospholipase A2γ of the instant invention (claim 1 phospholipase A2γ does not have any structural limitation) are one and the same and therefore inherently possess the function to regulate energy storage.

Claims 1-2, 4-5, 7 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Tanaka et al., (Biochem. Biophysical Res. Commun., 2000, Vol. 272: 320-326, published June 07, 2000). Claims 1-2, 4-5, 7 and 40, are directed to an isolated nucleic acid molecule comprising the polynucleotide encoding a phospholipase A2γ polypeptide or an isolated polynucleotide having at least 90% sequence identity to SEQ ID NO: 6, vector and host cell comprising said polynucleotides. Tanaka et al., (*supra*) teach the isolation of a polynucleotide from human that has 90.8% homology to SEQ ID NO: 6 of the instant application and encoding a polypeptide having phospholipase A2γ activity that has 100% homology to SEQ ID NO: 1 of the instant application (see sequence alignment provided). Furthermore, the reference also teaches the recombinant expression constructs (expression vector pEF-BOS-FF driven by SV 40 promoter), host cells and method of making said polypeptide (Materials and Methods, page 320 and Results and Discussion, pages 321-324) and therefore, Tanaka et al., anticipate claims 1-2, 4-5, 7 and 40 as written.

Applicants' have traversed the rejections with the argument that: 1) Tanaka et al., describes an independent phospholipase A2 that predominantly exists in membrane fractions and exhibits a phospholipase A2 activity in a calcium-independent manner when expressed in COS-7 cells; and 2) Tanaka et al., do not describe or suggest an isolated nucleic acid molecule as recited in claim 1. More specifically, Tanaka et al., does not describe or suggest an isolated nucleic acid molecule that supplies at least one of fatty acids for β-oxidation and hydrolyzing lipids for signaling molecules to regulate energy storage.

Applicants' arguments have been considered and found to be non-persuasive. Reply for 1) & 2): 1) The polynucleotide isolated by Tanaka et al., having 90.8% homology to SEQ ID NO: 6 of the instant application and encoding a polypeptide having phospholipase A2γ activity that has 100% homology to SEQ ID NO: 1 of the instant application and therefore inherently posses al the biochemical characteristics of the isolated polypeptide and encoding polynucleotide of the instant invention. 2) Tanaka et al., in column 1, first paragraph, page 320 clearly state that when cells are stimulated, intracellular phospholipase A2 (PLA_2) cleaves membrane phospholipids at the sn-2 position to release arachidonic acid (well known in the art as signaling molecules and are involved in modulating many cellular functions) which directly activates various enzymes and further as admitted by the applicants' in the instant disclosure, page 2, first paragraph, lines 1-4. Examiner also takes the position that the signaling molecules generated by the catalytic activity of Phospholipase A2s (PLA2s) of Tanaka et al., disclosure and the phospholipase A2γ of the instant invention (claim 1 phospholipase A2γ does not have any structural limitation) are one and the same and therefore inherently possess the function to regulate energy storage.

Claims 1-5, 7, 8 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Mancuso et al., (JBC., 2000, Vol. 275 (14): 9937-9945, published April 07, 2000). Claims 1-5, 7, 8 and 40 are directed to an isolated nucleic acid molecule comprising the polynucleotide encoding a phospholipase A2γ polypeptide or an isolated polynucleotide having at least 90% sequence identity to SEQ ID NO: 6, vector and host cell comprising said polynucleotides. Mancuso et al., (*supra*) teach the isolation of a polynucleotide from human that has 100% homology to SEQ ID NO: 6 of the instant application and encoding a polypeptide having phospholipase A2γ activity that has 100% homology to SEQ ID NO: 1 of the instant application (see sequence alignment provided). Furthermore, the reference also teaches the recombinant expression constructs (expression vector pFASTBAC driven by SV 40 promoter), host cells and method of making said polypeptide (Fig. 1 and Results section, page 9939) and therefore, Mancuso et al., anticipate claims 1-5, 7, 8 and 40 as written.

Applicants' have traversed this rejection with the reasoning, Mancuso et al., does not describe or suggest an isolated nucleic acid molecule as recited in claim 1. More specifically, Mancuso et al., does not describe or suggest an isolated nucleic acid molecule that supplies at least one of fatty acids for β-oxidation and hydrolyzing lipids for signaling molecules to regulate energy storage.

Applicants' arguments have been considered and found to be non-persuasive. The polynucleotide isolated by Mancuso et al., (*supra*) teach the isolation of a polynucleotide from human that has 100% homology to SEQ ID NO: 6 of the instant application and encoding a polypeptide having phospholipase A2γ activity that has 100% homology to SEQ ID NO: 1 of the

instant application (see sequence alignment provided). Mancuso et al., in columns 1-2, page 9937, clearly state that phospholipases A2 catalyzes the esterolytic cleavage of fatty acids from the sn-2 position of phospholipids thereby regulating the release of lipid second messengers (e.g. eicosanoids and lysophospholipids), growth factors (lysophosphatic acid) and membrane physical properties and further as admitted by the applicants' in the instant disclosure, page 2, first paragraph, lines 1-4. Examiner also takes the position that the signaling molecules generated by the catalytic activity of Phospholipase A2s (PLA2s) of Mancuso et al., disclosure and the phospholipase A2γ of the instant invention (claim 1 phospholipase A2γ does not have any structural limitation) are one and the same and therefore inherently possess the function to regulate energy storage.

Maintained-Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 8, 16, 17 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al., (US Patent 5,625,125) in view of Tanaka et al., (published June 07, 2000) or Mancuso et al., (published April 07, 2000). Bennett et al., (*supra)* disclose the construction of a transgenic vector comprising the isolated polynucleotide encoding the phospholipase A2 enzyme/polypeptide, the truncated version of the said gene encoding the polypeptide and the use of the said vector in the generation of transgenic mice and rat expressing said polypeptides.

Bennett et al., does not specifically teach the vector comprised SEQ ID NO: 6, wherein the encoded polypeptide with phospholipase A2γ activity. Tanaka et al., or Mancuso et al., (*supra*) teach the molecular cloning and characterization of a polynucleotide from human origin that has 100% sequence homology to SEQ ID NO: 6 and encoding a polypeptide having phospholipase A2γ activity that has 100% sequence homology to SEQ ID NO: 1 of the instant application (see sequence alignment provided). It would have been obvious to a person of ordinary skill in the art to make a vector encoding phospholipase A2γ operably linked to the SV40 promoter for use in transgenic mouse as taught by Bennett et al., wherein the phospholipase A2γ polynucleotide sequence was SEQ ID NO: 6 taught by Tanaka et al., or Mancuso et al.. Those of ordinary skill in the art at the time of invention was made would have been motivated to make the phospholipase A2γ construct taught by Bennett et al., using the phospholipase A2γ sequence of SEQ ID NO: 6 of Tanaka et al., or Mancuso et al., to determine the function of phospholipase A2γ *in vivo*. Those of ordinary skill would have recognized that the transgenics could be used to identify compounds that modulate phospholipase A2γ activity. The expectation of success of merely making the vector is high, because methods for constructing transgenic vectors configured to express phospholipase in a transgenic mouse were well known in the art as supported by Bennett et al.

Claims 1-5, 7-8, 16-17, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bennett et al., (US Patent 5,625,125) and Tanaka et al., (published June 07, 2000) or Mancuso et al., (published April 07, 2000) and further in view of McTiernan et al., (US Patent No.: 5,917,123). The combination of Bennett et al., and Tanaka et al., or Mancuso et al., teaches a vector encoding phospholipase A2γ of SEQ ID NO: 6 operably

linked to the SV40 promoter for use in transgenic mice. Said combination does not teach the vector for use in transgenic mice further comprising a reporter gene encoding luciferase or a promoter controlling the expression of desired gene for myocardial specific expression. McTiernan et al., (*supra*) teach transgenic vector constructs comprising different MHC promoters driving the gene of interest including the reporter gene luciferase, specifically for expression of gene of interest in cardiac tissues and also method for generating a transgenic mouse with said constructs (entire document). It would have been obvious to a person of ordinary skill in the art to combine the teachings of Bennett et al., Tanaka et al., Mancuso and McTiernan et al., to produce a transgenic vector comprising the polynucleotide of Tanaka et al., or Mancuso et al., of SEQ ID NO: 6 linked to the a reporter gene encoding luciferase and a promoter controlling the expression of desired gene for myocardial specific expression of McTiernan et al. Motivation to do so derives from the fact that the vector design of McTiernan et al., et al., would result in efficient expression of gene of interest in target tissues such as cardiac tissues and to understand the pathological effects of overexpression of phospholipases in cardiac tissue as phospholipase A2 activity is implicated in the pathophysiology of cardiac tissue i. e., atherosclerosis (Bennett et al., column 6, lines 63-65). Such a transgenic mouse would also serve as animal model to test the inhibitors of phospholipases. The expectation of success is high, because methods for constructing transgenic vectors configured to express phospholipase in a transgenic mice were well known in the art and Bennett et al., Tanaka et al., Mancuso et al., and McTiernan et al., teach the methods and structural elements for making such a vector configured to generate a transgenic mice expressing phospholipase A2 ($TGiPLA_2$) mice and to express the phospholipase A2 in clinically significant tissues such as cardiac tissue.

The above references render claims 1-5, 7-8, 16-17, 37 and 40 *prima facie* obvious to one of ordinary skill in the art.

Applicants' have amended the claims and have argued that with the amendments none of the cited references render claims 1-5, 7, 8, 16-17, 37 and 40 obvious over prior cited references.

Reply: Applicants' arguments have been fully considered but are not deemed persuasive as the cited references indeed render the instant invention obvious over cited prior art, as the references provide the structural elements, method for constructing vectors for generation of transgenic mice, motivation and expectation of success.

Applicant's arguments are directed against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The cited references are in congruence with the obviousness rejection and teach all limitations of the instant claims i. e., meet all the criteria and parameters (Teaching, Suggestion and Motivation) as defined by *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling.

Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an Obviousness rejection. So long as the motivation or suggestion to combine the teaching of the cited references is known or disclosed in the prior art and is obvious to one skilled in the art. This is sufficient to establish a *prima facie* case of obviousness.

Therefore, the examiner continues to hold the position that the combination of the cited references renders the instant invention obvious for the following reasons. One of ordinary skill

in the art would have been motivated to make the phospholipase A2γ construct taught by Bennett et al., using the phospholipase A2γ sequence of SEQ ID NO: 6 of Tanaka et al., or Mancuso et al., to determine the function of phospholipase A2γ *in vivo*. One of ordinary skill in the art would have been motivated to combine these references because those of ordinary skill would have recognized that the transgenics could be used to identify compounds that modulate phospholipase A2γ activity and the expectation of success of merely making the vector is high, because methods for constructing transgenic vectors configured to express phospholipase in a transgenic mouse were well known in the art as supported by Bennett et al.

The basis for the examniner to continue to hold his position is reasoned below; examiner has provided unequivoical evidence for combining the cited references and that the cited references have been properly applied in this obviousness rejection in accordance with the factual enquires set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling. Furthermore the cited references teach all the limitations of the instant claims.

The cited references render claims 1-5, 7, 8, 16-17, 37 and 40 *prima facie* obvious to one of ordinary skill in the art when one applies the Teaching, Suggestion and Motivation (TSM) test under the rationale for arriving at a conclusion of obviousness as suggested by the KSR ruling. The rationale applied for this rejection is as follows:

(1) Combining prior art elements according to known method to yield predictable results.

(2) Simple substitution of one known element for another to obtain predictable results.

(3) "Obvious to try"- choosing from a finite number of identified, predictable solution, with a reasonable expectation of success.

The instant invention is a simple combination of elements taught in the prior art, wherein the elements of prior art are combined to yield predictable results and the choice is from a finite number of identified elements with a highly predictable outcome and expectation of success.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claims 8, 37 and 40 are objected to, due to informalities.

2. Claims 1-2, 4-5, 7, 8, 16-17 and 40 are rejected for failing to comply with 35 U.S.C. 112 first paragraph for enablement and written description.

3. Claims 1-2, 4-5, 16, 17 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al., (US Patent 5,625,125).

4. Claims 1-2, 4-5, 7, 8 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Tanaka et al., (Biochem. Biophysical Res. Commun., 2000, Vol. 272: 320-326, published June 07, 2000) and Claims 1-5, 7, 8 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Mancuso et al., (JBC., 2000, Vol. 275 (14): 9937-9945, published April 07, 2000).

5. Claims 1-5, 7, 8, 16-17, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bennett et al., (US Patent 5,625,125), Tanaka et al., (published June 07, 2000) or Mancuso et al., (published April 07, 2000) and in further view of McTiernan et al., (US Patent No.: 5,917,123).

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Applicants must respond to the rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Claims 1-5, 7-8, 16-17, 37 and 40 are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
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Apr. 25, 2008.

/Rebecca E. Prouty/
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